Answer 1:

Bibliographic Information

In vivo selection of human hematopoietic cells in a xenograft model using combined pharmacologic and genetic manipulations. Pollok, Karen E.; Hartwell, Jennifer R.; Braber, Annemarije; Cooper, Ryan J.; Jansen, Michael; Ragg, Susanne; Bailey, Barbara J.; Erickson, Leonard C.; Kreklau, Emiko L.; Williams, David A. Department of Pediatrics, Herman B Wells Center for Pediatric Research, The Riley Hospital for Children, Indianapolis, IN, USA. Human Gene Therapy (2003), 14(18), 1703-1714. Publisher: Mary Ann Liebert, Inc., CODEN: HGTHE3 ISSN: 1043-0342. Journal written in English. CAN 140:230134 AN 2003:969275 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Strategies that increase the ability of human hematopoietic stem and progenitor cells to repair alkylator-induced DNA damage may prevent the severe hematopoietic toxicity in patients with cancer undergoing high-dose alkylator therapy. In the context of genetic diseases, this approach may allow for selection of small nos. of cells that would not otherwise have a favorable growth advantage. No studies have tested this approach in vivo using human hematopoietic stem and progenitor cells. Human CD34+ cells were transduced with a bicistronic oncoretrovirus vector that coexpresses a mutant form of O6-methylguanine DNA methyltransferase (MGMTP140K) and the enhanced green fluorescent protein (EGFP) and transplanted into nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice. Mice were either not treated or treated with O6-benzylguanine (6BG) and 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). At 8-wk postinjection, a 2- to 8-fold increase in the percentage of human CD45+EGFP+ cells in 6BG/BCNU-treated vs. nontreated mice was obsd. in the bone marrow and was assocd. with increased MGMTP140K-repair activity. Functionally, 6BG/BCNU-treated mice demonstrated multilineage differentiation in vivo, although some skewing in the maturation of myeloid and B cells was obsd. in mice transplanted with granulocyte-colony stimulating factor (G-CSF)-mobilized peripheral blood compared to umbilical cord blood. Expansion of human cells in 6BG/BCNU-treated mice was obsd. in the majority of mice previously transplanted with transduced umbilical cord blood cells. In addn., a significant increase in the no. of EGFP+ progenitor colonies in treated vs. nontreated mice was obsd. in highly engrafted mice indicating that selection and maintenance of human progenitor cells can be accomplished by expression of MGMTP140K and treatment with 6BG/BCNU.

Answer 2:

Bibliographic Information

Sensitization of pancreatic tumor xenografts to carmustine and temozolomide by inactivation of their O6-methylguanine-DNA methyltransferase with O6-benzylguanine or O6-benzyl-2'-deoxyguanosine. Kokkinakis, Demetrius M.; Ahmed, Mansoor M.; Chendil, Damodaran; Moschel, Robert C.; Pegg, Anthony E. Department of Pathology and the Cancer Institute, The University of Pittsburgh, Pittsburgh, PA, USA. Clinical Cancer Research (2003), 9(10, Pt. 1), 3801-3807. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 140:210081 AN 2003:847716 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Adenocarcinoma of the pancreas is refractory to chemotherapeutic agents, including BCNU and streptozotocin. We have previously shown that drugs, which adduct the O6-position of guanine, are ineffective against pancreatic tumor cell lines because of high expression of O6-methylguanine-DNA methyltransferase (MGMT). The effect of MGMT inactivation on the resistance of pancreatic tumors to carmustine (BCNU) and to temozolomide (TMZ) was examd. in five human pancreatic tumor xenografts in athymic mice. Tumor-bearing mice were treated: (a) with a single i.p. injection of BCNU or TMZ at the max.-tolerated doses of 75 and 340 mg/m2, resp.; and (b) with O6-benzylguanine (BG) or O6-benzyl-2'-deoxyguanosine (dBG) in combination with BCNU or TMZ. Pretreatment with the MGMT inactivators BG or dBG reduced the max.-tolerated doses of BCNU and TMZ to 35 and 170 mg/m2, resp. MIA PaCa-2, CFPAC-1, PANC-1, CAPAN-2, and BxPC-3 having MGMT levels of 890, 1680, 680, 900, and 330 fmol/mg protein, resp., were unresponsive to BCNU. MIA PaCa-2 and CFPAC-1 were also unresponsive to TMZ, whereas CAPAN-2 responded with a tumor delay of 32 days. BG or dBG sensitized all tumors to both BCNU and TMZ. BG plus BCNU treatment of MIA PaCa-2, CFPAC-1, PANC-1, CAPAN-2, and BxPC-3 induced tumor delays of 18, 16, 12, 14, and 16 days, resp. In comparison, dBG plus BCNU at doses that were

equitoxic to BCNU plus BG yielded tumor delays of 30, 19, 16, 21, and 22 days, resp. The pancreatic tumors tested displayed functional mismatch repair that, however, may not be always sufficiently restrictive to prevent mutations under alkylation stress. Treatments with either BCNU or TMZ resulted in some degree of mutation in recurring tumors with the exception of CAPAN-2, the only wt-p53 xenograft. DBG, a weak MGMT inactivator in vitro as compared with BG, was markedly more effective than the latter in enhancing the efficacy of BCNU against pancreatic tumor xenografts.
Both BG and dBG also enhanced the efficacy of TMZ against pancreatic tumors, possibly because of the repression of MGMT, which cannot be achieved with TMZ treatments alone. These results suggest that pancreatic tumors, which are resistant to DNA alkylating agents, may be sensitized to such agents when pretreated with MGMT inactivators.

Answer 3:

Bibliographic Information

Synergy between methionine stress and chemotherapy in the treatment of brain tumor xenografts in athymic mice. Kokkinakis, Demetrius M.; Hoffman, Robert M.; Frenkel, Eugene P.; Wick, Jacquelynn B.; Han, Qinghong; Xu, Mingxu; Tan, Yuying; Schold, S. Clifford. Department of Neurological Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA. Cancer Research (2001), 61(10), 4017-4023. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 135:205104 AN 2001:401936 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

This study describes a novel approach to the treatment of brain tumors with the combination of recombinant L-methionine-α-deamino-γ-lyase and chemotherapeutic regimens that are currently used against such tumors. The growth of Daoy, SWB77, and D-54 xenografts in athymic mice was arrested after the depletion of mouse plasma methionine (MET) with a combination of a MET- and choline-free diet and recombinant L-methionine-α-deamino-γ-lyase. The treated tumor-bearing mice were rescued from the toxic effects of MET withdrawal with daily i.p. homocystine. This regimen suppressed plasma MET to levels below 5 μM for several days, with no treatment-related deaths. MET depletion for 10-12 days induced mitotic and cell cycle arrest, apoptotic death, and widespread necrosis in tumors but did not prevent tumor regrowth after cessation of the regimen. However, when a single dose of 35 mg/m2 of N,N'-bis(2-chloroethyl)-N-nitrosourea (BCNU), which was otherwise ineffective as a single therapy in any of the tumors tested, was given at the end of the MET depletion regimen, a more than 80-day growth delay was obsd. for Daoy and D-54, whereas the growth of SWB77 was delayed by 20 days. MET-depleting regimens also trebled the efficacy of temozolomide (TMZ) against SWB77 when TMZ was given to animals as a single dose of 180 mg/m2 at the end of a 10-day period of MET depletion. The enhanced responses of both Daoy and SWB77 to DNA alkylating agents such as BCNU and TMZ could be attributed to the down-regulation of O6-methylguanine-DNA methyltransferase activity. However, the synergy of MET depletion and BCNU obsd. with D-54 tumors, which do not express measurable O6-methylguanine-DNA methyltransferase protein, is probably mediated by a different mechanism. MET depletion specifically sensitizes tumors to alkylating agents and does not significantly lower the toxicity of either BCNU or TMZ for the host. In this regard, the combination approach of MET depletion and genotoxic chemotherapy demonstrates significant promise for clin.
evaluation.

Answer 4:

Bibliographic Information

Development of human lymphoma/leukemia xenograft models in immune-deficient mice for evaluation of potential anticancer agents. Dykes, D. J.; Hollingshead, M. G.; Camalier, R. F.; Waud, W. R.; Mayo, J. G. Southern Research Institute, Birmingham, AL, USA. Contributions to Oncology (1999), 54(Relevance of Tumor Models for Anticancer Drug Development), 295-304. Publisher: S. Karger AG, CODEN: COONEV ISSN: 0250-3220. Journal written in English. CAN 133:217399 AN 2000:242563 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Eleven human lymphoma/leukemia cell lines were assessed as in vivo xenograft models in severe combined immunodeficient (SCID) mice. In prepn. for efficacy evaluations of new antitumor agents, all eleven cell lines have been characterized for sensitivity to known clin. useful agents. The lines included in the study represent a variety of diseases including T-cell, myelogenous, and lymphoblastic leukemias, as well as histiocytic, B-cell and Burkitt's lymphomas. The selected agents for this study were representative of various chem. classes. Addnl., growth studies were performed including comparisons in athymic nude mice. These studies were designed to det. s.c. tumor vol. doubling times, graft success, latent growth periods, and other characteristics necessary to effectively implement and interpret anticancer efficacy evaluations. The various tumor lines used proved to be good models for chemotherapy trials. In the chemotherapy trials, considerable independent chemotherapeutic profiles were obsd. but there were also some similarities among the various histol. types.

Answer 5:

Bibliographic Information

In vitro and in vivo inhibition of glioblastoma and neuroblastoma with MDL101731, a novel ribonucleoside diphosphate reductase inhibitor. Piepmeier, Joseph M.; Rabidou, Nicole; Schold, S. Clifford, Jr.; Bitonti, Alan J.; Prakash, Nellikunja J.; Bush, Tammy L. Dep. of Surgery/Neurosurgery, Yale Univ. Sch. of Medicine, New Haven, CT, USA. Cancer Research (1996), 56(2), 359-61. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 124:164570 AN 1996:60555 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We examd. the effects of MDL101731, a novel ribonucleoside reductase inhibitor, against human glioblastomas and neuroblastoma, both in vitro and in xenograft models, to det. its activity against malignant brain tumors. MDL101731 produced a concn.-dependent inhibition of both glioblastoma cell lines (HS683 and J889H) and neuroblastoma (SK-N-MC) in nanomolar concns. (IC50, 30-90 nM).s.c. xenografts of human glioblastoma (D54) in athymic mice increased to five times their initial vol. at a median of 7.4 days in control animals, while tumor regression occurred in 12 of 12 animals treated with MDL10173 (100 mg/kg, i.p., two times/wk). S.c. xenografts during 22 days of treatment ($P < 0.0001$). Intracerebral implants of D54 carried a median survival of 20 days in control animals, whereas animals receiving MDL101731 (100 mg/kg, i.p., two times/wk, days 10-35) had a median survival of 46.5 days ($P < 0.0001$). Intracerebral xenografts of SK-N-MC in athymic mice resulted in a median survival of 23 days in control animals and 26 days in animals treated with carmustine (1,3-bis(2-chloroethyl)-1-nitrosourea 20 mg/kg/wk, i.v. $\times$ 2; difference not significant). There was 90% survival in animals treated with MDL101731 (200 mg/kg, i.v., two times/wk, days 7-35) up to 90 days after implant. These studies indicate that MDL101731 has potent antiproliferative activity against human malignant brain tumors.

Answer 6:

Bibliographic Information

Preliminary experimental results with the nitrosourea derivative ACNU in the treatment of malignant gliomas. Bamberg, Michael; Budach, Volker; Stuschke, Martin; Gerhard, Lieselotte. Dep. Radiat. Oncol., West Ger. Tumour Cent., Fed. Rep. Ger. Radiotherapy and Oncology (1988), 12(1), 25-9. CODEN: RAONDT ISSN: 0167-8140. Journal written in English. CAN 109:47958 AN 1988:447958 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The cytotoxic effectiveness of the nitrosureas ACNU (Nimustine) and BCNU (Carmustine) were compared at equitoxic doses in xenografts from 2 astrocytomas grades III/IV (Li, Re) and 1 oligodendroglioma grade III (Oe) in nude mice. Growth delays of 18.7 days (ACNU) and 2.4 days (BCNU) for the Li-xenograft were obsd. at an LD10 for both drugs. For the Re- and Oe-xenografts, growth delays of 18.0 vs. 14.0 days and >27.0 vs. 14.2 days were obsd. at an 33 mg/kg of ACNU or BCNU, i.p., resp. Apparently, there is a therapeutic advantage with ACNU for these high grade gliomas.

Answer 7:

Bibliographic Information

An experimental study of xenografted human gliomas. Bloom, H. J. G.; Bradley, N. J.; Davies, A. J. S.; Richardson, S. G. Inst. Cancer Res., R. Marsden Hosp., London, UK. Editor(s): Walker, Michael D.; Thomas, David G. T. Biol. Brain Tumour, Proc. Int. Symp., 2nd (1986), Meeting Date 1984, 415-21. Publisher: Nijhoff, Boston, Mass CODEN: 55JOAH Conference written in English. CAN 106:113248 AN 1987:113248 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Chemotherapy of human astrocytomas growing as s.c. xenografts in mice revealed that the Grade III tumors were relatively insensitive but that agents such as procarbazine [671-16-9] and BCNU [154-93-8] were capable of procuring significant growth delay when used to treat Grade IV tumors. Against Grade IV tumors growing intracerebrally, procarbazine and BCNU were also effective agents but not in all animals. In a preliminary series of expts. surgical resection was shown to augment tumor growth rates which could be reduced by perioperative adjuvant chemotherapy.

Answer 8:

Bibliographic Information

Xenografts in pharmacologically immunosuppressed mice as a model to test the chemotherapeutic sensitivity of human tumors. Floersheim, G. L.; Bieri, A.; Chiodetti, Nicole. Zent. Lehre Forsch., Kantonssp., Basel, Switz. International Journal of Cancer (1986), 37(1), 109-14. CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 104:81665 AN 1986:81665 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A human tumor xenograft model using pharmacol. immunosuppressed mice was assessed for its suitability to test preclinically the sensitivity of colorectal carcinomas, bone sarcomas and melanomas against anticancer agents. Beside ionizing radiation, 14 cytotoxic drugs including 5-fluorouracil (5-FU) [51-21-8], dimethylmyleran (DMM) [55-93-6], cytosine arabinoside [147-94-4], cyclophosphamide [50-18-0], melphalan [148-82-3], mitomycin C [50-07-7], adriamycin [23214-92-8], bleomycin [11056-06-7], etoposide [33419-42-0], vinblastine [865-21-4], cisplatin [15663-27-1], procarbazine [671-16-9], DTIC [4342-03-4], and BCNU [154-93-8] were assayed. Ionizing radiation, 5-FU and DMM were also applied at LDs followed by bone-marrow rescue high-dose therapy. Four colon carcinomas responded poorly to most of the agents but one tumor displayed marked sensitivity to BCNU. LDs of radiation, 5-FU and DMM and cyclophosphamide and by an osteosarcoma to the latter drug. No strong effects were seen against melanomas. LDs of DMM induced the best regression of one colon carcinoma. In general, the superiority of high-dose therapy for solid human tumors compared to maximally tolerated doses was demonstrated. Individual carcinomas of the same type displayed different drug sensitivity.

Answer 9:

Bibliographic Information

Renal cell carcinoma - xenotransplantation into immuno-suppressed mice. Kopper, L.; Magyarosy, E.; Nagy, P.; Lapis, K.; Szamel, I.; Eckhardt, S.; Csata, S.; Wabrosch, G.; Repassy, D. 1st Inst. Pathol. Exp. Cancer Res., Semmelweis Med. Univ., Budapest, Hung. Oncology (1984), 41(1), 19-24. CODEN: ONCOBS ISSN: 0030-2414. Journal written in English. CAN 100:150726 AN 1984:150726 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Twenty one human renal cell carcinomas (RCC) were xenotransplanted into artificially immunosuppressed mice. Four tumors grew successfully retaining some characteristics of the primary tumors (according to morphol. and karyotype anal.), but losing metastatic

capacity. One of the serially transplantable tumors (HT 40) with hyperdiploid cellular DNA content and estrogen receptor positivity failed to respond to the single maximally tolerated dose of several cytotoxic agents.

Answer 10:

Bibliographic Information

Chemotherapy and radiation therapy of human medulloblastoma in athymic nude mice. Friedman, Henry S.; Schold, S. Clifford, Jr.; Varia, Mahesh; Bigner, Darell D. Med. Cent., Duke Univ., Durham, NC, USA. Cancer Research (1983), 43(7), 3088-93. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 99:63962 AN 1983:463962 CAPLUS

Abstract

The human medulloblastoma cell line TE-671 was grown s.c. and intracranially in athymic nude mice. Tumor-bearing animals treated with chemotherapeutic agents or radiation were compared to untreated tumor-bearing controls. Tumors growing s.c. were sensitive to cyclophosphamide [50-18-0] and vincristine [57-22-7] with growth delays in duplicate trials of 15.8/16.5 and 12.9/15.0 days, resp. These tumors were minimally responsive to the 2,5-bis(1-aziridinyl)-3,6-dioxodiethyl ester of 1,4-cyclohexadiene-1,4-dicarbamic acid [57998-68-2] and cis-diamminedichloroplatinum II [15663-27-1] and unresponsive to methotrexate [59-05-2], NSC 351521 [72732-56-0], NSC 409962 [154-93-8], and procarbazine [671-16-9]. Radiation therapy with 2500 or 1500 rads as a single fraction produced a marked response, with growth delays of 39.5 and 21.1 days, resp. Cyclophosphamide produced a significant increase in the median survival of mice with intracranial tumors. Vincristine produced a minimal increase in the median survival while no response was seen to the 2,5-bis(1-aziridinyl)-3,6-dioxodiethyl ester of 1,4-cyclohexadiene-1,4-dicarbamic acid at the dose level and schedule tested. This model system will allow further anal. of the therapeutic sensitivity of human medulloblastoma to other agents or combined-modality regimens.

Answer 11:

Bibliographic Information

Human brain tumor xenografts in nude mice as a chemotherapy model. Houchens, David P.; Ovejera, Artemio A.; Riblet, Sylva M.; Slagel, Donald E. Battelle Mem. Inst., Columbus, OH, USA. European Journal of Cancer & Clinical Oncology (1983), 19(6), 799-805. CODEN: EJCODS ISSN: 0277-5379. Journal written in English. CAN 99:63770 AN 1983:463770 CAPLUS

Abstract

Two human brain tumors which were previously established in nude mice were used to det. antitumor efficacy of various therapeutic agents. These tumors were a medulloblastoma (TE-671) and a glioma (U-251) with mass-doubling times of 3.5 and 5.5 days, resp., as s.c. implants in nude mice. Intracranial tumor challenge was accomplished by inoculating tissue culture-grown cells of either tumor into the right cerebral hemisphere to a depth of 3 mm. Groups of mice which had been inoculated with tumor were treated with various doses and schedules of antineoplastic compds. by the i.p. route. A new drug (rapamycin [53123-88-9]) was very effective against the U-251 tumor. This model system should prove valuable in assessing the effects of various chemotherapeutic modalities against brain tumors.

Answer 12:

Bibliographic Information

Misonidazole enhancement of the action of BCNU and melphalan against human melanoma xenografts. Clutterbuck, R. D.; Millar, J. L.; McElwain, T. J. Div. Phys., Inst. Cancer Res., Sutton/Surrey, UK. American Journal of Clinical Oncology (1982),

5(1), 73-8. CODEN: AJCODI ISSN: 0277-3732. Journal written in English. CAN 96:174042 AN 1982:174042 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effects of combinations of BCNU [154-93-8] and misonidazole [13551-87-6], and melphalan [148-82-3] and misonidazole on growth delay in 2 human malignant melanoma xenograft lines grown in immune-deprived mice were investigated. Misonidazole on its own had no effect on the growth of these tumors, but combinations of BCNU-misonidazole and melphalan-misonidazole produced greater tumor growth delays than those produced by the cytotoxic drugs alone. This was accompanied by increased wt. loss. Misonidazole in combination with melphalan also increased hemopoietic stem cell toxicity, but in the case of BCNU there was no enhancement of bone marrow toxicity at the dose chosen for tumor expts.

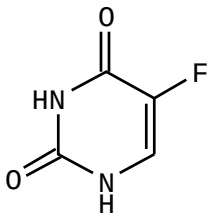
Answer 13:

Bibliographic Information

Studies in an animal model on the effectiveness of adjuvant chemotherapy with 5-FU and BCNU in cases of colorectal adenocarcinoma. Schmitz, R.; Hueiper, J.; Pichlmayr, R. Klin. Abdom. Transplantationschir., Med. Hochsch. Hannover, Hannover, Fed. Rep. Ger. Journal of Cancer Research and Clinical Oncology (1981), 100(2), 213-20. CODEN: JCROD7 ISSN: 0171-5216. Journal written in English. CAN 95:73492 AN 1981:473492 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effect of combined chemotherapy with 5-FU (5-fluorouracil) (I) [51-21-8] and BCNU [154-93-8] on well-differentiated human adenocarcinomas of different stages following xenotransplantation and growth in syngeneic balb/c nude mice collectives was investigated. With a tumor take of approx. 90%, marked remissions of ≤43% of the original vol. were obtained only with those transplant tumors initially classified as Dukes A and B; carcinomas graded Dukes C/D underwent no significant remission. Pathohistol. findings during tumor remission revealed large amts. of fibrotic tissue, together with surviving nests of tumor cells.



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Answer 14:

Bibliographic Information

Experimental study of combination therapy against human glioma xenograft by differentiation-inducing agent and cytotoxic chemotherapeutic drug. Shi Ming-gang; Huang Qiang; Dong Jun; Sun Zhi-fang; Lan Qing Department of Neurosurgery, Brain Tumor Research Laboratory, Second Affiliated Hospital of Suzhou University, Suzhou 215004, P. R. China. szqhdnah@pub.sz.jsinfo.net Ai zheng = Aizheng = Chinese journal of cancer (2002), 21(10), 1090-4. Journal code: 9424852. ISSN:1000-467X. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Chinese. PubMed ID 12508650 AN 2003002637 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND & OBJECTIVE: Cytotoxic agent remains the main chemotherapeutic drug for glioma, although it has many limitations. It is not known whether differentiation-inducing agent can enhance antitumor efficiency of cytotoxic agent. This study was designed to investigate anti-tumor effects of differentiation-inducing agent in combination with cytotoxic chemotherapeutic drug against glioma. METHODS: Poorly-differentiated human brain glioma xenografted nude mice were treated with carmustine(1, 3-bis-(2-chloroethyl)-1-nitrosourea, BCNU) and sodium phenylbutyrate (SPB). The therapeutic effects were determined by measuring of tumor size, pathological changes, different phases of cell cycle of tumor cell proliferation, expression of differentiation antigen, and tumor cell apoptosis. RESULTS: The therapeutic effects of SPB plus BCNU group were much better than that of SPB or BCNU group alone, which were proved by lower growth rate of the tumor, cellularity decreasing, appearance of astroid-like polyglonal cells, G0/G1 ratio increasing, upregulation of GFAP expression. CONCLUSION: Combined application of SPB and BCNU can obviously inhibit proliferation of glioma, and promote differentiation of tumor cells.